

### **REMARKS**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Claims 18, 20, 23, 36, 38, 41, 43, 45, and 47 have been amended, claims 1-17 and 24-35 have been cancelled, and claims 53-55 have been added. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Thus, claims 18-23, and 36-55 are pending in the application. Support for new claims 53-55 can be found in paragraph [0033] of the specification. No new matter has been added.

In addition, the Applicant would like to thank Examiners Crow and Johannsen for their comments and suggestions in the telephonic interview held February 21, 2008. In particular, the independent claims have been amended to claim *nucleotide* concentrations *in* the inlet and outlet chambers and wherein the measured difference in the concentration is *proportional* to the amount of nucleotide incorporated into a newly synthesized strand complementary to the nucleic acid molecule.

### **Claim Objections**

Claims 20, 38, 43, and 47 are objected to because each of the claims recites the limitation “concentrations of nucleotides is” in lines 1-2 of each of the claims. Claims 20, 38, 43, and 47 have been amended to recite “nucleotides are.” This objection should be withdrawn in light of this Amendment.

**Claim Rejections - 35 USC § 112, First Paragraph**

Claims 18-23 and 36-52 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner the word “unknown” was new matter. This rejection should be withdrawn in light of this Amendment as the word “unknown” has been deleted.

**Claim Rejections - 35 USC § 112, Second Paragraph**

Claims 18-23 and 36-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 18, 36, 41, and 45 have amended to change “first” and “second” channels to “inlet” and “outlet” channels. Claims 41 and 45 have been amended to change “the” to “a”. Additionally, claims 41 and 45 have been amended to clarify the “first” and “second” Raman detection units. Claim 43 has been amended to remove “inlet” channel. These rejections should be withdrawn in light of these Amendments.

**Claim Rejections - 35 USC § 103**

Claims 18-22, 36-39, and 41-52 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273) in view of Davis (U.S. Patent No. Publication No. US 2002/0102595) and in view of Natan (U.S. Patent Publication No. US 2002/0142480). Claims 23 and 40 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273) in view of Davis (U.S. Patent Publication No. US 2002/0102595) in view of Natan (U.S. Patent No. Publication No. US

2002/0142480) as applied to claims 18 and 36, and further in view of Ogle (U.S. Patent No.

6,328,869). Applicants respectfully traverse these rejections.

Independent claims 18, 36, 41, and 45 have been amended to include the limitation “wherein a difference between the first concentration of nucleotide and the second concentration of nucleotide is proportional to the amount of nucleotide incorporated into a newly synthesized strand complementary to the nucleic acid.” Support for this limitation can be found in paragraph [0033] of the specification. None of the applied reference disclose this feature. Shipwash teaches reversibly immobilizing a labeled ternary complex in the reaction chamber. As the reaction progresses a new ternary complex is formed which displaces the labeled ternary complex. The displaced ternary complex is detected. (Shipwash [378]). Davis discloses a two zone detection system in which the incorporation of a nucleotide triphosphate (NTP) onto an immobilized enzyme-nucleic acid is detected by the absence of a signal in the second zone. (Davis [0055]-[0062]). That is, Davis only teaches an apparatus that determines the absence or presence of an NTP. Natan discloses methods of making free-standing SERS active nanoparticles. (Natan [0016]). None of the references teach or suggest the detection of a change in concentration. Further, none of the reference alone or in combination teach or suggest measuring a first concentration in an inlet channel upstream of a reaction chamber, measuring a second concentration in an outlet channel downstream of the reaction chamber, and determining the amount of nucleotide incorporated into a newly synthesized strand complementary to a nucleic acid in the reaction chamber by determining the difference in concentration between the inlet and out channels.

Independent claims 18, 36, 41, and 45 have been amended to include the limitation “wherein the first or second Raman detection unit is capable of detecting at least one *unlabeled* nucleotide at a

*single nucleotide level.*” This limitation is supported by claim 19 (now canceled) as well as paragraph [0111] which states, “[s]ingle nucleotides can be detected by SERS using a 100  $\mu\text{m}$  or 200  $\mu\text{m}$  microfluidic channel.” The single nucleotides disclosed in paragraph [0111] are unlabeled nucleotides as explained in paragraph [0115] of the specification. Prior to this invention, nobody had been able to detect *single unlabeled* nucleotides by SERS as explained in paragraph [0015] of the specification, which states: “This the first report Raman detection of unlabeled nucleotides at the single nucleotide level.”

In short, Applicants have been the first to have been able to detect a single unlabeled molecule of nucleotide (dAMP) as shown in Table I of the specification. This result would have been *totally unexpected* at the time of this invention. “One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of ‘unexpected results,’ *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.” *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). In the present case, as in *In re Soni*, Applicants respectfully submit that the claimed apparatus is capable of detecting a single nucleotide, which would have been totally unexpected, and this should suffice to establish unexpected results in the absence of evidence to the contrary. 54 F.3d at 751, 34 USPQ2d at 1688.

#### **Obviousness-Type Double Patenting**

Claims 18-19, 21, 36-37, 41-42, and 45-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-28 and 30 of copending Application No. 11-753,361 in view of Shipwash (U.S. Patent Application Publication

No. US 2002/0058273) in view of Davis (U.S. Patent No. Publication No. US 2002/0102595) and in view of Natan (U.S. Patent No. Publication No. US 2002/0142480).

Applicants respectfully request this rejection be held in abeyance pending indication of patentable subject matter.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: June 6, 2008

Respectfully submitted,

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